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Original Research

The relationship between dialysis adequacy and COVID-19 onset and mortality risk: Single center experience

The impact of dialysis inadequacy in hemodialysis patients with COVID-19 disease

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Abstract
Aim: We primarily aimed in this study was to evaluate risk factors for COVID-19 infection and if any association between dialysis inadequacy in COVID-19 infection in maintenance hemodialysis (MHD) patients. Secondly aimed to describe prevalence and risk factors associated with long-lasting symptoms of non-deceased COVID-19 MHD patients before vaccination.
Material and Methods: One hundred one MHD patients infected with COVID-19 and 100 MHD patients without the infection were enrolled in this retrospective cross-sectional study. Risk factors for mortality, need to intensive care unit (ICU) stay and long-lasting symptoms were analyzed.
Results: The mean age of patients was 59.13±13.58 years. COVID-19 infected patients had significantly higher number of patients with DM, COPD, CHF. The need for ICU was found to be statistically significantly higher in patients with COPD and DM. In our results, the patients who had lower Kt/V at admission hospital had more than 5 fold higher rate of COVID-19 those have higher Kt/V. We analyzed risk factors for mortality at, one year included higher age, higher CRP and lower base-line Kt/V were diagnostic criteria. Older MHD patients had a high frequent of long-lasting symptoms. Low Kt/V, low hemoglobin level and high CRP level associated with a higher risk of long-lasting symptoms (p=0.00, p=0.001, p=0.02)
Discussion: We conclude that DM, CHF, COPD, older age, obesity were poor prognostic factors for in infected with COVID-19. Dialysis adequacy parameters of Kt/V, serum albumin level, hemoglobin level were significantly lower in need to ICU and deceased patients.

Keywords
Hemodialysis, Dialysis Adequacy, COVID-19 Disease, Mortality

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Introduction

Coronavirus disease 2019 (COVID-19) was declared as a pandemic by the World Health Organization (WHO) on March 2020. COVID-19 presents as asymptomatically or can cause a variety of infection findings from mild infection to severe pneumonia [1,2,3].

Patients with kidney disease appear to be at high risk for COVID-19 and it is related complications, as most of them are older-age and have multiple co-morbidities such as hypertension, diabetes, and cardiovascular diseases. Dialysis patients have additional risk factors, including chronic immune dysfunction, the need to go to the hospital for hemodialysis three times a week and these comorbidities increase the risk of developing severe types, need to ICU and mortality of COVID-19 infection [4,5,6].

COVID-19 disease's pathophysiological mechanism is poorly understood but various studies have reported that infected patients have an abnormal level of cytokines. Inflammation is associated with the progression of the disease and poor clinical outcomes [7].

Globally dialysis adequacy has recognized a combination of the following parameters, middle molecule clearance, control of mineral metabolism, anemia correction, and quality of life. Mostly, clinicians have used Kt/V for measurement of dialysis adequacy [8].

Dialysis dose as measured by Kt/V can be affected by many factors, including; treatment time (TT), blood flow rate (BFR), dialysate flow, hypotension , vascular access function, dialyzer characteristics and proper blood sampling . In the literatüre some of the studies have demonsrated that lower than recommended Kt/V may increase mortality, especially in females [9,10]. Many studies have reported that, inflammation is closely related to dailysis adequacy [11].

In this study, we primarily aimed to determined risk factors for COVID-19 infection, need to ICU and mortality rate among the MHD patients and aims to document if a relationship exists between dialysis inadequacy and COVID-19 infection in MHD patients.

Material and Methods

Our study was designed retrospectively. COVID-19 was diagnosed according to the Turkey Ministry of Health COVID-19 guideline. A total of 201 patients undergone maintenance hemodialysis (MHD) for at least 3 months were recruit this study; 78 patients were confirmed COVID-19 cases, 23 suspected (PCR test negative but chest computer tomography, positive) and 100 non-infected COVID-19 control hemodialysis patients. The exclusion criterias were patients with incomplete data and hematological or hemostatic disease. For each patient, the following clinical parameters were recorded from the medical file: age, gender, primary kidney disease, co-morbidities, complaints during hospitalization, vital signs at the time of admission, chest computer tomography (CT) findings during admission, COVID-19 PCR results. Charlson's comorbidity index (CCI) calculated was used to calculate CCI score and estimated 10-year survival. And also routine blood examinations included complete blood count, coagulation profile, and serum biochemistry (including liver function tests, total proteins, albumin, ferritin, pro-calcitonin, C-reactive protein (CRP), ferritin, D-dimer, white blood cell (WBC), lymphocyte), Kt/V and UF volume.

Hypoalbuminemia was defined as serum albumin level was <3.5 g/dl (N: 3.5-5.5 g/dl) Serum CRP level < 10 mg/L was considered normally. The weekly average Kt/V were used to dialysis adequacy parameters. The accuracy of dialysis (Kt/V) was calculated according to the following formula: - ln (R-0.008*T) + (4-3.5*R) * 0.55 * UF/V.

The data of Kt/V were analyzed by taking a mean of last three months before COVID-19 infection and admission to hospital due to COVID-19 infection.

All of the patients received standard therapy according to the Turkey Ministry of Health COVID-19 guideline. We used favipiravir 2 × 1600 mg as loading and 2 × 600 mg as maintenance all of the confirmed and suspected covid-19 patients for 5 or 10 days. The other treatment modalities such as high dose vitamin C, immune plasma, antibiotic, glucocorticoids, tocilizumab, were recorded. The patients have an abnormal gas exchange (partial pressure of oxygen saturation of inspired; paO2 <300 or arterial blood oxygen <400) or the patients who had higher serum CRP, ferritin, corticosteroids, and/or tocilizumab were added to treatment.

The patients were divided in two groups to according to COVID-19 situations; the positive real time-PCR confirmed groups and COVID-19 suspected group with negative real time PCR and the non-infected hemodialysis patients for control groups.

This study was approved by the Bahcesehir University Faculty of Medicine Ethical Commite (2022-03/12). The study is compliant with the guidelines of the Declaration of Helsinki.

Statistics:

SPSS software (version 22.0, SPSS Inc. Chicago, IL, USA) was used for statistical analysis were performed. The Kolmogorov-Smirnov test was used to detect normality in the data distribution. Descriptive analyses were given as mean and standard deviations for normally distributed variables.

The Mann-Whitney U test was used to compare differences in nonparametric data between the groups. For comparing parameters without normal distribution student T-test was used. Ci-Square test was used for comparing the categorical variables. P-value less than 0.05 was considered to have statistical significance. We used t-tests, analysis of variance (MANOVA), multivariate Cox regression analysis, and x^2 tests to compare data for most continuous, categorical variables by COVID-19 status.

Results

The study groups consisted of 78 patients confirmed, 23 suspected COVID-19 and 101 non-infected COVID-19 MHD patients. Demographic and clinical parameters of all MHD patients are shown in table 1. The mean age of patients 59± 13.58; % 58.7 were male and the mean dialysis duration time was 59.58±47.41 months. In infected with COVID-19 group hypertension %43, Diabetes Mellitus (DM) %51.5, congestive heart failure (CHF) %30, chronic obstructive pulmonary disease (COPD) %38.4 patients were. The most common symptom is cough (%61), fever (%38), myalgia (%34) in infected COVID-19

patients. All of the patients were hospitalized in the confirmed and suspected COVID-19. Eighty-three patients had pulmonary involvement (68 bilateral, 15 unilateral). Eighty-eight patients required oxygen support and thirty-four patients were transferred to the intensive care unit (ICU)

To find risk factors for COVID-19 disease among MHD patients; patients infected with COVID-19 were compared to patients who were non-infected with COVID-19. (Table 2) Confirmed and suspected COVID-19 patients were statistically significant lower Kt/V (p= .04), higher CCI score (p= .03), lower estimated 10 years survival (p= .01) and lower hemoglobin levels (p= .01) COVID-19 infected patients had significantly higher number of patients with DM (p= .01), COPD (p= 0.04), CHF (p= .02). In our results the patients those had lower Kt/V at admission hospital had more than 5-fold higher rate of COVID-19 those have higher Kt/V. (p=.00)

Patients who needed to stay at ICU were compared to patients who did not. The need for ICU was found to be statistically significant higher in patients with COPD (p= .01) and DM (p= .03). Patients who needed ICU stay had higher CCI score (p= .04), lower estimated 10-year survival (p= .01) and lower Kt/V (p= 0.03). They also had statistically significantly lower lymphocyte (p= .02), lower oxygen saturation (p= .01), higher WBC (p= .03), higher CRP (p= .00), and higher bilateral pulmonary involvement (p= .00) at admission.

In our results, the patients who had lower Kt/V at admission hospital had a more than 5-fold higher rate of Covid-19 those have higher Kt/V.

The mortality rate in our study cohort was %31.6. The deceased patients were older (>65 y.o.) (p= .01). COPD and DM were the most common co-morbid conditions in deceased patients (respectively p=.00, p=.06, p=.02). CRP and Ferritin values were found to be significantly higher, albumin level was significantly lower in the non-survival groups. (p= .04, p= .03, p= .00, p= .01, p=.02) Patients who deceased had statistically significantly lower Kt/V. (p= .04). Non-survival patients had statistically significant higher CCI score (p= .02), lower estimated 10-year survival (p= .00). There was no statistically significant difference for gender to compared deceased and survival patients. There were no statistically significant differences in mortality rate

Table 1. Demographic and clinical parameters all of the MHD patients.

Variables	
Age (year)	59.13±13.58
Male n (%)	58.7
Body mass index (kg/m²)	24.41±58
Dialysis vintage (month, mean±SD)	59.58±47.1
Diabetes Mellitus (%)	49
Hypertension (%)	45.8
Congestive heart failure (%)	28
Chronic Obstructive Pulmonary Disease (%)	16,8
CCI score (mean±SD)	5.2
Charlson's Co-morbidity Index	
Estimated 10-year survival %	32.31±24.85
Kt/V	1.49
UF volume (liter)	2.9
C-reactive protein (CRP) (mg/L)	24.66±21.85
Ferritin (ug/L)	338.66±169.66
White Blood Cell (WBC, 10^9/L mean±SD)	8.643±1.873
Lymphocyte (10^9/L, mean±SD)	1.37±0.64
Albumin (g/dl)	3.64±0.42
Hemoglobin (g/dl, mean±SD)	10.96±0.99
Erytropoetin dosage (IU month, mean±SD)	5880±2949
Pulmonary Involvement (n:83)	
Bilateral involvement	68
Unilateral involvement	15

Table 2. Comprasion of demographic and laboratory parameters with and without COVID-19

Variables	COVID-19 (-) (n: 100)	COVID-19 (+) (n:101)	P
Age (year)	58.12±23.72	59.64±25.23	0.3
Male n (%)	53	46	0.2
Body mass index (kg/m)	23.58±6.1	24.91±4.65	0.1
Dialysis vintage (month, mean±SD)	61.8±33.1	58.75±39.6	0.2
Diabetes Mellitus (%)	38	51.5	0.01
Hypertension (%)	48	43	0.1
Congestive heart failure (%)	24	30	0.02
Chronic Obstructive Pulmonary Disease (%)	24	38,4	0.04
CCI score (mean ±SD)	4.50±2.18	5.59±1.75	0.02
Estimated 10-year survival %	18.1	10.1	0.00
Kt/V	1.7±0.3	1.35±0.4	0.04
URR (%, mean±SD)	75.5	68.8	0.03
UltrafiltrationF vlome (Liter)	2.9	2.8	0.2
C-reactive protein (CRP) (mg/L)	14±26	35±22	0.03
Ferritin (ug/L)	282.8±108.3	367±200	0.01
White Blood Cell (WBC, 10^9/L mean±SD)	8.73±1.73	8.68±1.82	0.04
Lymphocyte (10^9/L, mean±SD)	1.81±0.67	1.2±0.97	0.1
Albumin (g/dl, mean±SD)	3.78±0.48	3.57±0.42	0.02
Hemoglobin (g/dl, mean±SD)	11.12±1.43	10.85±1.27	0.01
Erythropoietin dosage (IU month, mean±SD)	5715±2819	5963±3015	0.06
25 (OH) vitamin D (ng/ml, mean±SD)	17.21±9.91	16.8±10.2	0.07

Data are means ±SD (median) or number (%). URR: urea reduction ratio, CCI: Charlon's co-morbidity index. Statistically, significant value is p<0.05.

Table 3. Associations Between Clinical Characteristics and Mortality Among MHD Patients with COVID-19

Variables	%95 CI	p
Age		
<65	1.22 (0.84-2.52)	0.4
>65	0.75 (0.43-1.55)	0.02
Body Mass Index	1.74 (1.39-2.75)	0.01
DM	1.32 (0.97-1.87)	0.02
COPD	1.11 (1.58-0.87)	0.00
Kt/V	0.88 (0.38-1.1)	0.04
UF volume (liter)	1.08 (0.45-1.12)	0.6
CRP (g/dl)	0.90 (0.71-1.38)	0.03
Ferritin	1.1 (1.87-2.34)	0.00
Albumin <3.5 g/dl	1.1 (0.98-1.88)	0.02
Corticosteroid	1.65 (1.09-2.48)	0.2
Tociluzimab	1.12 (0.78-1.55)	0.09

Clinical and other parameters associated with mortality was analyzed using the Cox regression model. The statistically significant value is p<0.05. WBC: White Blood Cell, CRP: C-reactive Protein, COPD: Chronic Obstructive Pulmonary Disease, UF: Ultrafiltration.

between patients who used corticosteroids and tocilizumab and did not use them. (p=.2, p= .09) Table 3.

We did not find any difference during the hospitalized period mead week pre-dialysis serum potassium, phosphate, and bicarbonate values in confirmed COVID-19, suspected COVID-19 patients, and non-infected COVID-19 patients.

In the end, we were compared to patients who died due to other causes in non-infected patients with deceased COVID-19 patients who had statistically significantly lower Kt/V, higher WBC, ferritin, D-dimer levels in infected COVID-19 patients. (p= .03, p= .01, p= .00 respectively.)

In the multivariable method (Manova), older age (> 65 years), lower Kt/V, higher CRP, high CCI score, and along with DM, COPD significantly associated with the need to ICU.

In our results, one year mortality rate was 41.5 % (42 of 101 patients). 31 of 101 of died during hospitalization period. 3 of 42 (7.14 %) in the first six months, of these 2 died from heart attack, one from cerebrovascular event. Eight of 42 patients died in the followed six months. These of 3 died from respiratory failure, 2 of these from cerebrovascular event, 3 of these from heart attack.

The 12 month mortality rate for non-covid hemodialysis patients was 12 of 100 (12%) and one year mortality rate was lower than COVID-19 MHD patients (p= 0.032). The patients in COVID-19 who were died older than who survived (p=0.042) and more frequently had a positive pulmonary involvement in chest tomography. During the one year follow-up period; 23 of the 59 patients (38.9%), suffered at least one additional event, including respiratory, cardiovascular or non-specific general symptoms (e.g. fatigue, myalgia).

We analyzed risk factor for mortality at, one year included higher age, higher CRP and lower base-line Kt/V were diagnostic criteria (retrospectively p= 0.03, p= 0.01, p=0.00).

At 12 months, 13 (22.4 %) patients showed having at least one long-lasting symptoms. The most common long-lasting symptoms were muscle weakness, cough and breath-shortness. The patients who were having long-lasting symptoms were older age and higher CRP levels than others.

Discussion

COVID-19 is an infectious disease caused by a new coronavirus (SARS-CoV-2) and can progress from variables symptoms such as fever, dry cough, joint pain, severe picture such as shortness of breath, respiratory failure, and multiple organ dysfunction syndromes. The main risk groups for mortality and developing complications during the COVID-19 pandemic are older age and people with chronic health problems [11] .

Dialysis adequacy is described by clinical and laboratory measures along with solute clearance. These are including the following parameters; blood pressure control, uremic symptoms, inflammatory markers, serum albumin, and hemoglobin levels, metabolic acidosis, urea reduction ratio (URR), and Kt/V [12,13,14].

In our study, we primarily aimed to detect the presence of any difference in dialysis inadequacy between COVID-19 MHD patients and non-infected COVID-19 MHD patients. We secondarily aimed to define the possible relation of dialysis adequacy and other laboratory parameters or co-morbidities in COVID-19 MHD patients.

A few studies reported that Kt/V inadequacy (< 1.2) is associated with a chronic inflammatory state [11]. The increase of Kt/V 0.1 is associated with a reduced risk of mortality from cardiovascular, cerebrovascular, and infectious diseases [15].

Among dialysis patients, those had lower Kt/V at admission hospital had a more than 5 fold higher rate of COVID-19 those who have higher Kt/V, a pattern that although commented on, has not been well quantified in national studies. Also, we did find a statistically significant association with lower Kt/V and need to ICU and mortality rate among the COVID-19 MHD patients. Therefore we describe that dialysis inadequacy is an important risk factor for mortality among the COVID-19 MHD patients.

In many studies reported that chronic inflammation is an important factor for inadequate dialysis and HD dosage (Kt/V) has been shown to have a significant impact on the morbidity and mortality rate in patients on MHD patients [11]. Additionally in the literature has been reported that the occurrence of inflammation is higher in patients who were on dialysis for a long time [16]. But in our study, there was no statistically significant relationship between Kt/V and dialysis vintage.

Although, dialysis inadequacy is related to a more extended hospitalization time and higher medical costs, 3 while the inverse denotes effective patient hemodialysis [17]. In our study we did not find an association between hospital stays and Kt/V, serum albumin, or CRP levels in infected with COVID-19 MHD patients.

Serum albumin and hemoglobin levels are used as parameters of dialysis adequacy in MHD patients [18]. According to our results, serum albumin and hemoglobin level were statistically significant higher in infected with COVID-19 MHD patients. However, we did not find associations were observed between serum albumin, hemoglobin level and need to ICU stay. Within the groups of patients non-survived, the mortality rate was higher in a patient with low albumin levels.

UF volume is another important marker for dialysis adequacy in MHD patients [19,20]. The median UF was 2.9 liters in our study groups. We did not find any differences in compared MHD patients infected with and non-infected with COVID-19 for UF volume.

Until now, there have been many reports of COVID-19 disease in MHD patients. Can et al, showed that risk factors that were significantly associated with infection risk were older age, higher CCI score, and lower estimated 10-year survival [21]. In our study risk factors for COVID-19 infection were lower Kt/V, lower hemoglobin level, higher CCI score, diabetic nephropathy, COPD, and CHF.

During the first time of pandemic, some of the studies indicated that corticosteroids caused delayed viral clearance, on the other hand, a few authors observed prescribing corticosteroids in COVID-19 patients [22,23,24]. The RECOVERY trial was showed that corticosteroids were a clear beneficial effect for viral clearance in COVID-19 patients [25].

According to our results, the patients receiving corticosteroids, the mortality rate was similar to non-receiving corticosteroids patients. Hyperglycemia and seconder bacterial infection were more frequent in corticosteroid receiving patients.

In this study, 101 MHD patients diagnosed with COVID-19,

33.6% of them were transferred to the ICU. It is seen that there is a positive correlation between advanced age (<65 y.o.) and ICU requirement. And also it has been shown that mortality risk related to COVID-19 was significantly higher in older age (>65), and in patients with higher CRP, ferritin, and WBC. Also, mortality risk significantly rises in patients with diabetic nephropathy, COPD, CHF.

The main difference is in our study from the other studies published until now the low Kt/V value, which is an indicator of dialysis adequacy, increases both the mortality ris, the need for ICU and high risk of long-lasting symptoms associated COVID-19.

Conclusion:

In our knowledge, this study is the first that investigates the relationship between Kt/V and inflammation in COVID-19 MHD patients and non-infected MHD patients. We detect a significant difference among Kt/V between the COVID-19 MHD patients and non-infected MHD patients. We claim that adequate and effective dialysis treatment both reduces the risk of being infected with COVID-19 in MHD patients and reduces the risk of intensive care unit need and mortality in MHD patients infected with COVID-19.

Our study has several limitations; firstly this was a retrospective study and limited participiants number . Some of the data such as changes in blood pressure, oxygen saturation, residual renal function, body weight, D-dimer and IL-6 levels were not included in the data. And also we do not evaluated antibody seroposivity for ımmunglobulin M (Ig M) and ımmunglobulinG (Ig G).

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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